influence treatment outcome or treatment toxicity. Furthermore, no enhanced RBE was found for FFF compared to FF photon beams.

PD-0186

Carotid intima-medial thickness as a marker of radiation-induced atherosclerosis

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Purpose/Objective: Radiotherapy to collateral structures such as the carotid artery leads to atherosclerosis and increased stroke risk. Arterial thickening is a precursor to atherosclerosis. Carotid intima-medial thickness (CIMT), a measure of arterial thickening, is a validated surrogate for prediction of cardio- and cerebrovascular events. Its application in irradiated arteries as a measure of accelerated atherosclerosis has shown variable results. This study investigates CIMT as an early marker of radiation-induced damage in head and neck cancer patients.
Materials and Methods: Patients with head and neck cancer treated with a wedged-pair and matched neck technique or hemi-neck radiotherapy (unirradiated (unirr) side as control) at least 2 years previously were included. Patients had been prescribed a dose of at least 50 Gy to the neck. CIMT was measured on B-mode ultrasound using semi-automated detection software. Measurements were taken from the far wall in 4 arterial segments: proximal- (prox), mid-, distal (dist) common carotid artery (CCA), and bifurcation and were compared to corresponding segments in the unirr artery. CIMT measurements >75th percentile of a reference normal population were considered abnormal and at increased cardiovascular risk.
Results: 24 patients (16 males) with a median age of 58 yrs (interquartile range (IQR) 49.2 – 64.2) were included. The mean maximum dose to the irradiated (irr) artery was 61.2 Gy (IQR 52.6 – 61.8) and 1.1 Gy (IQR 1.0 – 1.8 Gy) to the unirr carotid artery. Mean CIMT was significantly greater in irr carotid arteries compared to unirr arteries: mid-CCA (0.75mm ± 0.2 (irr) vs 0.64mm ± 0.12 (unirr) (P = 0.0057), distal CCA (0.79mm ± 0.24 (irr) vs 0.64mm ± 0.14 (unirr) (P = 0.005), and bifurcation (0.85mm ± 0.28 (irr) vs 0.7mm ± 0.17 (unirr) (P = 0.0231). For the irr prox CCA, 23/24 (95.8%) had a CIMT > 75th percentile vs 16/24 (66.7%) for unirr prox CCA. For irr mid CCA, 20/24 (83.3%) had CIMT >75th percentile vs 15/24 (62.5%) for unirr mid CCA. 21/24 (87.5%) of irr dist CCA CIMT was >75th percentile vs 11/24 (45.8) for unirr dist CCA. For irr bifurcation, 15/21 (71.4%) had a CIMT >75th percentile vs 11.24 (45.8%) for unirr bifurcation.
Conclusions: CIMT is increased in irr carotid arteries, suggesting this may be a useful marker of radiation-induced carotid atherosclerosis. The proximal CCA appears to be less sensitive to radiation-induced damage.

PD-0187

Hyperbaric oxygen therapy for late adverse events after particle radiotherapy

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Purpose/Objective: This is the first report on the application and outcomes of hyperbaricoxygen therapy (HBO) for late adverse events which developed after proton or carbon-ionbeam radiation therapy.
Materials and Methods: Between April 2008 and May 2012, 40 patients underwent HBO for late adverse events (105 episodes of 8 events) which developed more than 5 months after particle radiotherapy. There were 24 male and 16 female patients aged 15-83 years (median: 67 years), and the performance state (PS) at the initiation of HBO was: PS0:PS1:PS2:PS3= 0:24:13:3. The primary diseases treated with particle radiotherapy were head-and-neck tumor in 23 patients, prostate cancer in 8, bone soft tissue tumor in 5, liver cancer in 4, and lung metastasis in 1. The late adverse events treated with HBO were classified into 8 events using CTC-AEver. 4.0. HBO was performed 3 times or more weekly, as a rule. The HBO chamber was compressed with 100% oxygen to 2.0 ATA inside, and the duration of treatment (pressure-keeping time) was 60 minutes. Responder of HBO was defined as a case of improvement in CTC-AE score.

Results:

Before HBO						
Event	n	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematuria	4	0	1	3	0	0
Rectal bleeding	6	0	0	6	0	0
Pain	32	0	6	20	6	0
Central nervous necrosis	4	0	1	2	1	0
Mucosal ulcer or fistula	22	0	3	11	8	0
Mandibular bone necrosis	18	0	2	11	5	0
Trismus	13	0	1	10	2	0
Skin ulcer	6	0	0	0	4	2

After HBO						
Event	n	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematuria	4	1	3	0	0	0
Rectal bleeding	6	3	1	1	1	0
Pain	32	5	10	12	4	1
Central nervous necrosis	4	0	2	1	1	0
Mucosal ulcer or fistula	22	0	4	10	7	1
Mandibular bone necrosis	18	0	3	9	4	1
Trismus	13	0	3	7	3	0
Skin ulcer	6	0	0	0	4	2

HBO was initiated 5-64 months (median: 19 months) after particle radiotherapy. The total number of HBO was 4-120 (median: 29). Table shows grading score of late adverse events before and after HBO. Response rate (number of responder/total cases) of 8 events was: hematuria, 100% (4/4); rectal bleeding, 67% (4/6); pain, 56% (18/32); central nervous necrosis, 50% (2/4); mucosalulcer or fistula, 36% (8/22); mandibular bone necrosis, 28% (5/18); trismus, 15% (2/13); and skin ulcer, 0% (0/9). Total response rate was 40% (43/105). The average number of HBO was significantly higher in responder (69±48.9) than in non-responder (44±27.9) groups (p=.001). Adverse events due to ABO were minimal. Otitis media (non-infectious) occurred in 14 patients (35%) (Grade 1in 12 (30%), Grade 2 in 1 (2.5%) and Grade3 in 1 (2.5%)). TIA, diarrhea, bronchitis, cerebral infarction and sinusitis occurred in each one patient, however these events were transient and HBO did not be discontinued.
Conclusions: HBO was effective for late radiation disorders after particle radiotherapy especially in hematuria, rectal bleeding, pain, and central nervous necrosis. Total response rate was 40% (43/105). It was suggested that many times (69±48.9) applications of HBO are necessary to obtain an effect.

PD-0188

Assessing the uncertainty in clinical dose-response outcomes with a bootstrap analysis

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Purpose/Objective: Numerous studies investigate the normal tissue dose-response relation. However, limited numbers of patients per study and the low incidence of toxicities render the relation uncertain. The aim of this study is to apply a statistical bootstrap analysis to evaluate the uncertainty in the predicted dose-response due to sampling variability.
Materials and Methods: Two clinical endpoints were considered: myelopathy of the cervical spinal cord and pneumonitis. Data was taken from the recently published QUANTEC review. In order to evaluate the uncertainty in the clinical data, a Monte Carlo-based bootstrap analysis was applied. Ten thousand bootstrap replicates of the original dataset were produced by random sampling with replacement. This simulates alternative outcomes at each dose in a different sample of patients of the same size from the same population. The analysis requires only the dose, the number of patients, and the number of occurrences of the studied endpoint. The dose reported in the QUANTEC review was used: the equivalent dose given in 2-Gy fractions (EQD2) for the spinal cord, and the mean dose for the lung. Two dose-response models, a Poisson-based model and the Lyman model, were fitted to each bootstrap replicate using maximum likelihood.
Results: The bootstrap analysis generates a family of curves representing the range of plausible dose-response relations. The 95% confidence intervals of the curve families for the two models overlap for doses included in the clinical study, but diverge beyond that. For higher doses, the Lyman model indicates a steeper slope than does the Poisson-based model. The bootstrap distributions of the model parameters D_{50} and γ (m) indicate negative (positive) correlation. For both data sets, the likelihood of the observed data was higher for the Lyman model. This result was robust over the bootstrap analysis with higher likelihood of the Lyman model for over 90% of the bootstrap replicates, in both data sets.